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(54) Title: DAPSONE AND PROMIN FOR THE TREATMENT OF DEMENTIA

(57) Abstract

This invention pertains to the novel use of 4,4'-diaminodiphenylsulfone and its didextrose sulfonate derivative and other closely related sulfones in the treatment of dementia (Alzheimer's disease). A method of treating dementia in a human being characterized by administering to the human being a therapeutic daily to weekly amount of a substance selected from the group consisting of 4,4'-diaminodiphenylsulfone, its didextrose sulfonate derivative, and other closely related sulfone derivatives, and therapeutically acceptable salts thereof.

DAPSONE AND PROMIN FOR THE TREATMENT OF DEMENTIA

This invention pertains to the novel use of 4,4'-diaminodiphenylsulfone and its didextrose sulfonate derivative and closely related anti-lepromatous sulfones in the treatment of dementia (Alzheimer's disease) in human beings.

Alzheimer's Disease is by far the most common cause of primary dementia. Either by itself, or in combination with multiple infarcts, it accounts for almost 80% of all cases. No treatment has been established which will prevent the onset or delay the progression of Alzheimer's Disease. It is possible that known drugs would have an as yet unrecognized efficacy in this respect.

4,4'-diaminodiphenylsulfone (Dapsone™) and its didextrose sulfonate derivative (Promine™) were first shown to have a favourable effect in treating rat leprosy in 1941 (Cowdry and Ruangsiri, Arch. Pathol. 32:632, 1941). Successful clinical trials for the treatment of human leprosy followed and these two components are now the most important anti-leprosy drugs. The two drugs have since been used for treating a variety of skin diseases such as dermatitis herpetiformis and efficacy has been reported in several disorders of presumed autoimmune origin such as rheumatoid arthritis, lupus erythematosus and Behcet's disease. Dapsone™ is a drug that has been used worldwide for over 40 years. It has been found to have few side effects and these are well understood due to extensive experience with patients taking the drug continuously for many years. To the applicants' knowledge, 4,4'-diaminodiphenylsulfone and its didextrose sulfonate derivative, and closely related antilepromatous sulfones have never been used or considered for the treatment of dementia.

Leprosy is no longer a fatal disorder, due in substantial measure to treatment with Dapsone™. It has anti-inflammatory action, which may seem paradoxical for

treatment of an infectious disease. However. M. leprae survives in macrophages, and one of the deleterious consequences of the infection, which is reduced by Dapsone, is widespread amyloidosis. Dapsone has also been reported to be effective for the treatment of various presumed autoimmune diseases, including dermatitis herpetiformis, rheumatoid arthritis, temporal arteritis, polymyalgia rheumatica, cutaneous lupus erythematosus, Behcet's disease and polyarteritis nodosa. The alternative antileprosy drugs, clofazimine and rifampicin, have also been reported to have efficacy in anti-inflammatory therapeutic applications.

SUMMARY OF THE INVENTION

The invention pertains to a method of treating dementia in a human being which comprises administering to the human being a therapeutic amount daily to weekly of a substance selected from the group consisting of 4,4'-diaminodiphenylsulfone, glucosulfone sodium (the didextrose sulfonate derivative of 4,4'-diaminodiphenylsulfone), and all closely related sulfone derivatives including, as examples, but not restricted to, sulfoxone sodium, sulfetrone sodium, and thiazolsulfone, and therapeutically and pharmaceutically acceptable salts thereof.

The substance can be effectively administered to the human being at dosage rates which can vary widely, and on schedules which can vary from twice daily to once weekly. The substance can be either 4,4'-diaminodiphenylsulfone, its didextrose sulfonate derivative, other closely related derivatives as mentioned above or pharmaceutically acceptable salts thereof. Typical therapeutic dosages will be in the range of 2 to 20 micromoles per kg body weight per day, and the preferred route will be oral.

The invention also pertains to a composition useful for treating dementia comprising substances selected from the group consisting of 4,4'-diaminodiphenylsulfone, the didextrose sulfonate derivative of 4,4'-diaminodiphenylsulfone, sulfoxone sodium, sulfetrone sodium, thiazolsulfone and all closely related sulfone derivatives, and pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

The invention is also pertains to an article of manufacture characterized by packaging material and a pharmaceutical agent characterized by 4,4'-diaminodiphenylsulfone), and all closely related sulfone derivatives including, as examples, but not restricted to, sulfoxone sodium, sulfetrone sodium, and thiazolsulfone, and therapeutically and pharmaceutically acceptable salts thereof, wherein the packaging material includes a notification which indicates that the pharmaceutical agent can be used for treating dementia in a human being in a therapeutic amount.

DRAWINGS

In the drawings:

Figure 1 represents a block graphical comparison of dementia percentage among treated and untreated patients from the age of 65 to over 85.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT OF THE INVENTION

Immunohistochemical studies on Alzheimer brain tissue have suggested a chronic inflammatory process may play a role in the observed neuronal degeneration. Dapsone™, 4,4'-diaminodiphenylsulfone, is effective in several chronic inflammatory disorders.

Leprosy patients are almost universally treated with 4,4-diaminodiphenylsulfone (Dapsone™), the didextrose sulfonate derivative (Promin™), or other closely related sulfonic derivatives, over prolonged periods. As a result of such treatment, and the availability of these drugs, leprosy is no longer fatal, and in many cases apparent cures can lead to drug withdrawal. The applicants have noted unexpectedly that the incidence of dementia (Alzheimer disease) amongst elderly leprosy patients being treated with either of the two drugs noted has been unusually low.

The applicants have conducted a formal survey of leprosy hospitals in Japan and have determined that there was significantly less prevalence of dementia amongst Dapsone™ and Promin™ treated leprosy patients compared with those who had been off such drugs for at least five years. It has therefore been concluded that Dapsone™ and Promin™, when administered on a daily dosage basis to the elderly patient, have a preventative action against dementia.

One of the inventors observed that on the Japanese island of Nagashima, leprosy patients seemed to have a low prevalence of dementia. Patients on this island live independently, but are under close medical supervision.

In a survey of thirteen national and three private leprosy hospitals in Japan, the incidence of dementia in patients 65 years and over was determined according to whether they were still receiving continuous treatment with 4,4'-diaminodiphenylsulfone, its didextrose sulfonate derivative or other anti-leprosy drugs, had received intermittent treatment, or no drug treatment with such chemicals over the previous five years.

The overall prevalence of dementia was 2.9% of the 1,410 patients 65 years and over continuously treated cases observed. This compares with 4.83% of 621 intermittently treated cases and 6.25% of 1,761 cases untreated for at least five years. Multiple logistic regression analysis showed a highly significant increase of dementia with age ($p = 0.0001$) and, after age adjustment, a significant reduction of dementia in patients on continuous drug treatment as compared with patients free of drugs for at least five years ($p = 0.017$). Treatment had no significant effect on the prevalence of strokes. The dementia figure for untreated cases was virtually double and compared closely with the figure of 6.25% reported by Shibayami et al. for the Japanese population over 65 years of age (Acta. Psychiat. Scand. 74:144-151, 1986). Statistical analysis of these data show that the probability of developing dementia is reduced to 63% by treatment with either Dapsone™ or Promine™. These data show preliminary evidence of the effectiveness of Dapsone™ and Promin™ in retarding the development of dementia.

Methods

Each institute was asked to categorize their elderly (65 years of age or over) patients according to age range and drug treatment over the past five years (continuously on Dapsone™, Promine™ or other anti-lepromatous drug; free of drug treatment; or on intermittent treatment). In each category, the total number of patients and the numbers with dementia or stroke were to be enumerated. In this survey, no attempt was made to identify the nature of the dementia except that persons who had had a clearly identified stroke in the absence of previous dementia were to be classed in the stroke, rather than the demented groups. In the treatment group overall, 1,240 (88%) had been treated with Dapsone, 53 (3.76%) with Promine, which is the didextrose sulfonate derivative of Dapsone, and the rest with

other antileprosy drugs. The percentages of demented were highly similar in these subgroups so that they were combined for analysis. The statistical analysis of the data was complicated by the sharp dependence of dementia on age and the failure of the groups to be precisely age-matched. Accordingly, the data on the treated and untreated groups were subjected to logistic regression analysis to determine their level of significance.

Results

The results for the treated, untreated and intermittently treated groups are summarized in Table 1:

TABLE 1

AGE RANGE	CASES TREATED FOR 5 YEARS					CASES NOT TREATED FOR 5 YEARS					INTERMITTENTLY TREATED CASES				
	Total No.	Demented No.	%	With Strokes No.	%	Total No.	Demented No.	%	With Strokes No.	%	Total No.	Demented No.	%	With Strokes No.	%
65-69	529	4	0.76	7	1.32	489	5	1.02	11	2.25	211	1	0.47	7	3.31
70-74	410	6	1.46	10	2.44	445	7	1.57	9	2.02	176	3	1.70	3	3.31
75-79	257	8	3.11	7	2.72	376	23	6.10	13	3.46	122	4	3.28	2	1.64
80-84	150	15	10.0	5	3.33	286	36	12.55	13	4.55	69	8	11.59	4	5.80
≥85	64	8	12.5	3	4.67	165	39	23.60	11	6.67	43	14	32.56	2	4.65
OVERALL															
≥65	1410	41	2.9	32	2.27	1761	110	6.25	57	3.24	621	30	4,83	18	2.90

The overall prevalence of dementia was 2.9% of the 1,410 continuously treated cases, 4.83% of the 621 intermittently treated cases, and 6.25% of the 1,761 cases untreated for at least five years. For stroke, the comparative figures were 2.27%, 2.90% and 3.24% respectively.

Statistical analysis showed that:

(a) There is a significant increase of dementia with age ($p = 0.0001$), with a logistic regression coefficient of 0.1721, but there is no age-by-treatment interaction ($p = 0.60$). This means that aging has the same effect on the prevalence of dementia in both groups and that the odds of developing dementia in either group increase at an annual rate of 18.8%.

(b) After adjustment for age,the effect of treatment is significant ($p = 0.017$), with a logistic regression coefficient of -0.4633. This means that the odds of developing dementia at any age are reduced by drug treatment to 63% of the corresponding odds in the untreated group (Figure 1.).

(c) After adjusting for age by logistic regression, treatment had no significant effect on the prevalence of strokes ($p = 0.30$); age, however, was highly significant ($p = 0.0002$), with a logistic regression coefficient of 0.0609, meaning that the odds of developing a stroke in either group increase at an annual rate of 6%.

The reason for hypothesizing that anti-inflammatory therapy might be effective in preventing or slowing down the progression of Alzheimer's Disease is the accumulation of evidence suggesting that a chronic inflammatory state of the brain exists in this disease. Reactive microglia, which are rarely seen in normal brain tissue, are abundant in Alzheimer's Disease brain tissue. They

strongly express class II major histocompatibility complex (MHC) glycoproteins, Fc receptors, and various β2 integrins which are complement receptors. There are also significant numbers of T cells in the tissue matrix. Brain tissue in affected areas is strongly stained by antibodies to a number of complement proteins, including Clq, C3d, C4d and the membrane attack complex C5b-9. This latter finding suggests that some of the neuronal degeneration in Alzheimer's Disease may be due to bystander lysis.

Therapeutic Dosage

Dapsone, Promine and closely related sulfones such as sulfoxone sodium, sulfetrone sodium and thiazolsulfone are all preferentially administered in oral tablet or enteric coated capsule form. Parenteral administration is possible, since some derivatives, such as Promine, are highly soluble in water, and can be prepared in ampules as an aqueous solution of up to 40% concentration. The dosages of sulfones and methods of administration for the retardation of dementia will be comparable to those now used for the treatment of leprosy and dermatitis herpetiformis. Typical dosages of Dapsone will vary from 100-200 mg once daily, to 200-400 mg twice weekly, to 300-600 mg once weekly. Tablets can be of any convenient size, but typically will be of 100 mg. Promine and other sulfones will be administered in equivalent molecular doses. As in leprosy, the drugs will be continued indefinitely. Lifetime treatment is anticipated.

WHAT IS CLAIMED IS:

1. A method of treating dementia in a human being characterized by administering to the human being a therapeutic daily to weekly amount of a substance selected from the group consisting of 4,4'-diaminodiphenylsulfone, the didextrose sulfonate derivative of 4,4'diaminodiphenylsulfone (glucosulfone sodium), and other closely related sulfone derivatives such as sulfoxone sodium, sulfetrone sodium and thiazolsulfone, and therapeutically and pharmaceutically acceptable salts thereof.

2. A method as claimed in claim 1 wherein the substance is administered to the human being at a daily dosage rate of between about 50 mg and 300 mg per day of Dapsone or its equivalent in molecular concentration for other sulfone derivatives.

3. A method as claimed in claim 1 wherein the substance is 4,4'-diaminodiphenylsulfone.

4. A method as claimed in claim 1 wherein the substance is the didextrose sulfonate derivative of 4,4'-diaminodiphenylsulfone.

5. A method as claimed in claim 1 wherein the substances are other closely related sulfone derivatives including sulfoxone sodium, sulfetrone sodium and thiazolsulfone.

6. A composition useful for treating dementia in a human being characterized by a substance selected from the group consisting of 4,4'-diaminodiphenylsulfone, the didextrose sulfonate derivative of 4,4'-diaminodiphenylsulfone, and other closely related sulfone derivatives, and pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

7. A composition as claimed in claim 6 wherein the substance is 4,4'-diaminodiphenylsulfone.

8. A composition as claimed in claim 6 wherein the substance is the didextrose sulfonate derivative of 4,4'-diaminodiphenylsulfone.

9. A composition as claimed in claim 6 wherein the substance is sulfoxone sodium, sulfetrone sodium, thiazolsulfone or other closely related derivatives of 4,4'-diaminodiphenylsulfone.

10. A composition as claimed in claim 6 wherein the substance is present in the composition in the range of about 10 mg. to 100 mg.

11. An article of manufacture characterized by packaging material and a pharmaceutical agent characterized by 4,4'-diaminodiphenylsulfone), and all closely related sulfone derivatives including, as examples, but not restricted to, sulfoxone sodium, sulfetrone sodium, and thiazolsulfone, and therapeutically and pharmaceutically acceptable salts thereof, wherein the packaging material includes a notification which indicates that the pharmaceutical agent can be used for treating dementia in a human being in a therapeutic amount.

12. An article as claimed in claim 11 wherein the pharmaceutical agent is in dosage quantities between 10 mg and 300 mg.

AMENDED CLAIMS

[received by the International Bureau on 28 September 1993 (28.09.93); original claims unchanged; new claims 13-17 (2 pages)]

7. A composition as claimed in claim 6 wherein the substance is 4,4'-diaminodiphenylsulfone.

8. A composition as claimed in claim 6 wherein the substance is the didextrose sulfonate derivative of 4,4'-diaminodiphenylsulfone.

9. A composition as claimed in claim 6 wherein the substance is sulfoxone sodium, sulfetrone sodium, thiazolsulfone or other closely related derivatives of 4,4'-diaminodiphenylsulfone.

10. A composition as claimed in claim 6 wherein the substance is present in the composition in the range of about 10 mg. to 100 mg.

11. An article of manufacture characterized by packaging material and a pharmaceutical agent characterized by 4,4'-diaminodiphenylsulfone), and all closely related sulfone derivatives including, as examples, but not restricted to, sulfoxone sodium, sulfetrone sodium, and thiazolsulfone, and therapeutically and pharmaceutically acceptable salts thereof, wherein the packaging material includes a notification which indicates that the pharmaceutical agent can be used for treating dementia in a human being in a therapeutic amount.

12. An article as claimed in claim 11 wherein the pharmaceutical agent is in dosage quantities between 10 mg and 300 mg.

13. The use of 4,4'-diaminodiphenylsulfone, the didextrose sulfonate derivative of 4,4'diaminodiphenylsulfone (glucosulfone sodium), or other closely related sulfone derivatives such as sulfoxone sodium, sulfetrone sodium and thiazolsulfone, and therapeutically and pharma-

ceutically acceptable salts thereof, in the manufacture of a pharmaceutical formulation for treating dementia in a human being characterized by administering to the human being a therapeutic daily to weekly amount of the formulation.

14. The use as claimed in claim 13 wherein the formulation is administered to the human being at a daily dosage rate of between about 50 mg and 300 mg per day of 4,4'diaminodiphenylsulfone or its equivalent in molecular concentration for other sulfone derivatives.

15. The use as claimed in claim 13 wherein the substance is 4,4'-diaminodiphenylsulfone.

16. The use as claimed in claim 13 wherein the substance is the didextrose sulfonate derivative of 4,4'-diaminodiphenylsulfone.

17. The use as claimed in claim 13 wherein the substances are other closely related sulfone derivatives including sulfoxone sodium, sulfetrone sodium and thiazolsulfone.

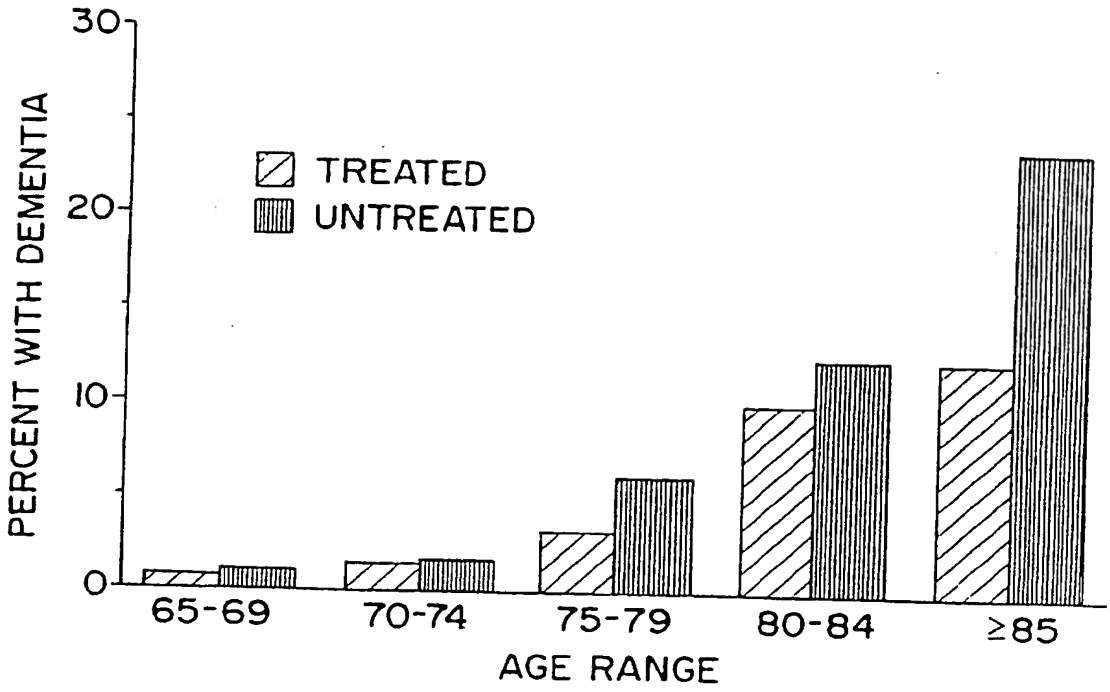

FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 92/00228

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/135; A61K31/70; A61K31/185; A61K31/425

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	DEMENTIA vol. 3, no. 3, 1992, pages 146 - 149 P.L. MCGEER ET AL. 'PREVALENCE OF DEMENTIA AMONGST ELDERLY JAPANESE WITH LEPROSY: APPARENT EFFECT OF CHRONIC DRUG THERAPY' see the whole document --- -/--	1-8, 10-12

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27 JANUARY 1993	16. 02. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	HOFF P.J.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	'THE MERCK INDEX' 1989 , MERCK & CO., INC. , RAHWAY, N.J., U.S.A. *Dapsone* see page 444 *Glucosulfone* see page 700 - page 701 *Solasulfone* see page 1372 *Sulfoxone sodium* see page 1416 *Thiazolsulfone* see page 1466	6-9
X	DE,A,3 923 088 (SAARSTICKSTOFF-FATOL GMBH) 24 January 1991 see the whole document	6-7,10

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

CA 9200228
SA 59597

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-3923088	24-01-91	None	